DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Alex Gorsky
Head of Pharma North America and Chief Executive Officer
Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

RE: NDA 20-823/21-025
Exelon® (rivastigmine tartrate) Capsules and Oral Solution
MACMIS ID #14943

WARNING LETTER

Dear Mr. Gorsky:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a professional file card (EXL-FC-0100-A) for Exelon® (rivastigmine tartrate) Capsules and Oral Solution (Exelon) submitted by Novartis Pharmaceuticals Corporation (Novartis) under cover of Form FDA-2253. The professional file card makes unsubstantiated superiority claims for Exelon, overstates the efficacy of Exelon, includes misleading risk presentations, and recommends or suggests a combination use of Exelon that has not been approved by FDA, and thus creates a new "intended use" for which the PI lacks adequate directions. Thus, the professional file card misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §§ 352(a) & (f)(1) & 321(n), and FDA implementing regulations. Cf. 21 C.F.R. 201.128. These violations are concerning from a public health perspective because they suggest that Exelon is safer or more effective than has been demonstrated, and they encourage the use of Exelon in circumstances other than those for which the drug has been shown to be safe and effective.

Background

The INDICATIONS AND USAGE section of the approved product labeling (PI) for Exelon states (in pertinent part):

> Exelon® (rivastigmine tartrate) is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

Exelon is also associated with numerous risks. The PI contains a bolded warning for gastrointestinal adverse reactions (including nausea and vomiting and weight loss), in addition to warnings concerning anorexia, peptic ulcers/gastrointestinal bleeding, concomitant use with anesthesia, effect on cardiovascular, pulmonary, and neurological systems (i.e., seizures), and risk of urinary obstruction. The PI also contains precautions for drug-drug interactions (i.e., use with anticholingeric and cholinomimetic medications, and other cholinesterase inhibitors). The most common adverse events (occurring at a rate of ≥5% and twice the placebo rate) reported in clinical trials in Alzheimer's patients were nausea, vomiting, anorexia, dyspepsia, and asthenia.

Unsubstantiated Superiority Claims

The file card makes several claims comparing the efficacy of Exelon to donepezil. For example, a two-page spread in the file card contains the following claims (pages 4 and 5):

- "In an open-label study, the majority of donepezil nonresponders responded to EXELON"
- "70% of donepezil nonresponders responded to EXELON in this open-label study - Response defined as no change or improvement in CGIC"[1]
- A pie chart entitled "RESULTS ON PRIMARY ENDPOINT," and accompanying text, which claims that "70% responded" (40% "improved" and 30% "stabilized") and 30% had "no response"

This presentation is misleading because, on the basis of an inadequate study, it suggests that Exelon is superior to donepezil in patients with mild-to-moderate Alzheimer's Disease who have not responded to donepezil. The claims in the file card are based on a 26-week, open-label, single-arm, uncontrolled trial of Exelon in 270 patients with mild-to-moderate Alzheimer's Disease whose earlier response to donepezil was judged to be poor.[2] The trial was inadequate in several respects. First, an open-label design is not suitable for evaluation of a subjective endpoint like CGIC (an observational scale that assesses the change from baseline in patients' degree of illness). Second, the study used a questionable definition of "response"; "response" included patients who demonstrated no change in CGIC.[3] Third, the study did not include a concurrent control group; rather, patients were compared to their own baseline, a kind of historical control. This design presumes, however, that patients could not have improved spontaneously, and does not evaluate what would have happened to patients given another treatment, such as placebo, or, more pertinently in this case, donepezil. There is good reason to believe patients' historical response might be different from their response in a formal study, either because conditions are different or because of observer

[1] Clinician's Global Impression of Change

[2] Figiel G, et al. Poster presented at: 57th Annual Scientific Meeting of the Gerontological Society of America; November 17-23, 2004; Washington, D.C.

[3] At the time of dissemination of the file card, donepezil was indicated for the treatment of mild to moderate dementia of the Alzheimer's type. Donepezil has since been approved for use in patients with severe Alzheimer's Disease as well.

expectations. A study designed to measure an effect in nonresponders to donepezil would randomize the non-responding patients in a double-blind study to either donepezil or Exelon.

Finally, the tagline "Efficacy matters most," which is presented in conjunction with the product name and logo throughout the file card, adds to the misleading impression that Exelon is more effective than donepezil. This presentation, in the context of the superiority claims discussed above, suggests that healthcare practitioners should prescribe Exelon because "efficacy" is the "most" important treatment consideration and Exelon is more effective than donepezil. FDA is not aware of substantial evidence or substantial clinical experience that demonstrates the superiority of Exelon over other Alzheimer's Disease treatment options. If you have such evidence, please submit it for review.

Overstatement of Efficacy

The file card is misleading because it suggests that Exelon is more effective than has been proven by substantial evidence or substantial clinical experience. Specifically, on page 6, the file card contains a graph under the heading, "EXELON HELPED SUSTAIN ADLs AT 26 WEEKS," showing the mean change in the effect on the Progressive Deterioration Scale (PDS) score (Exelon = 1.3, n=164; placebo = -1.9, n=208; $P<0.04$). Claims related to the efficacy of Exelon based on the secondary endpoint of PDS in this study are misleading because no method of analysis was specified for this measure in the protocol. Although multiple analyses were performed on a number of datasets, the cited p-value ($P<0.04$) was not adjusted for multiple comparisons; thus, the true significance of any finding is unknown. Furthermore, the PDS was used as a secondary efficacy measure in several major studies of Exelon (other than the referenced study), with inconsistent results. The presentation of the PDS data in the file card is particularly troubling, given the fact that FDA previously communicated the aforementioned issues regarding these data to Novartis.[4]

Second, on page 7, the file card contains misleading claims pertaining to the effect of Exelon on behavior. Specifically, a graph under the heading of "A RETROSPECTIVE SUBSET ANALYSIS IN POOLED STUDIES OF MODERATE AD PATIENTS" presents the percentage of patients (Exelon vs. placebo) with symptoms at baseline improving on the individual components of the Effect on Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) scale. In addition, the following claims are made:

- "Significantly reduced aggression at 26 weeks"

[4] The Division of Neurology Products has expressed the same concerns about these data to Novartis on more than one occasion. As detailed in the Medical Review conducted as part of the Approval Package for Exelon (publicly available at http://www.fda.gov/cder/foi/nda/2000/20823_Exelon.htm), Novartis first submitted the results of the Progressive Deterioration Scale (PDS) data as part of the original draft labeling. *See* Medical Review, at 48. On May 12, 1999, the PDS results were excluded from draft labeling attached to an approvable letter for the drug. *Id.* at 48. After the issuance of the approvable letter, at the sponsor's request, the Division agreed to reassess the PDS data. *Id.* However, the PDS results were again excluded from the final printed labeling for Exelon as of the date of the drug's approval on April 21, 2000. In the Medical Review, the Division expressed a series of concerns about the data and concluded that "it would appear appropriate for the Progressive Scale data to be deleted from labeling." *Id.* at 50.

- "Numerically reduced hallucinations and affective disturbance, diurnal rhythm, and activity disturbances after 26 weeks with daily dosages of 6 to 12 mg/day. Statistical significance was not shown"

This presentation is misleading in numerous ways because it implies that Exelon can help manage some behavioral aspects of Alzheimer's Disease when this has not been demonstrated by substantial evidence or substantial clinical experience. First, highlighting a non-significant finding is inherently misleading as the observation may be no more than a chance observation. Moreover, the BEHAVE-AD scale was not a designated primary or secondary efficacy measure in any of the three pooled studies. Instead, it was one of a number of parameters used by study investigators in determining and assigning scores for the CIBC-Plus (which was a primary efficacy measure), and no method of statistical analysis was prospectively specified for the BEHAVE-AD. Finally, the referenced retrospective pooled analysis was limited to a subset of 117 patients (5.5%) of a total of 2126 patients randomized in the three studies contained in the PI, including only patients whose baseline Mini Mental Status Exam (MMSE) score at study entry ranged from 10 to 12 (while the studies' MMSE inclusion criteria was a score of 10-26). Such subset analyses, representing a selection from dozens, perhaps hundreds, of possible subsets are subject to bias and are non-credible. The disclaimer that statistical significance was not shown is not sufficient to correct the misleading impression made by the claim.

Misleading Risk Presentation

The file card is also misleading because it suggests that Exelon is safer than has been demonstrated by substantial evidence or substantial clinical evidence. Exelon is associated with numerous serious risks. In particular, as stated in the WARNINGS section of the PI, Exelon use is associated with significant gastrointestinal adverse reactions relative to placebo, including nausea (47% vs. 12%), vomiting (31% vs. 6%), weight loss, and anorexia (17% vs. 3%).. In fact, severe vomiting was reported in 2% of Exelon-treated patients.

Page 3 and the back cover of the file card minimize the risks of Exelon therapy with claims such as:

- "Turn to EXELON for a favorable safety profile"
  - "No known pharmacokinetic drug-drug interactions (DDIs)"
    - "Cholinesterase inhibition not affected by Namenda® (memantine HCl)"
  - "No increased incidence in cardiac adverse events as measured by electrocardiogram (ECG)"

These presentations are misleading because they present positive information concerning the risks associated with Exelon but omit the serious and therapy-limiting risks associated with its use without reference to the presence and location elsewhere in the file card of a more complete discussion of risk information. We acknowledge the inclusion of risk information on page 11 of the file card; however, this presentation of risk information is insufficient to remedy the minimization of the risks associated with Exelon treatment by the aforementioned claims.

In addition to the above claims, the file card presents the following claims on page 8 (emphasis original):

- "**No** known pharmacokinetic DDIs" [with a checkmark under "Exelon"]
- "**No known pharmacokinetic interactions** with many commonly prescribed medications (eg, fluoxetine, warfarin, digoxin)"

These claims are misleading because they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. We acknowledge that pharmacokinetic interactions between Exelon and other medications are not expected.[5] However, as stated in the PRECAUTIONS section of the PI, Exelon is associated with drug-drug interactions, including interactions with anticholinergics, as well as with cholinomimetics and other cholinesterase inhibitors, which may be part of a treatment regimen for Alzheimer's Disease. By presenting claims concerning the lack of pharmacokinetic DDIs without the risks associated with the concomitant use of Exelon with anticholinergics, cholinomimetics, and other cholinesterase inhibitors, the file card misleadingly suggests that Exelon is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Similarly, the two-page spread on pages 8 and 9 of the file card, under the tab "Safety Profile," is misleading because it both omits and minimizes the risks associated with Exelon. This presentation contains numerous claims regarding Exelon's "safety profile," including "Turn to EXELON with confidence" and "EXELON HAS A SAFETY PROFILE THAT PROVIDES CONFIDENCE" with an accompanying table. The fact that the presentation is under the tab entitled "Safety Profile" implies that it provides an accurate summary of the "Safety Profile" for the drug; however, the presentation omits serious risks associated with the use of Exelon, including the bolded warning regarding gastrointestinal adverse reactions. Furthermore, because the use of Exelon is associated with these serious risks, to characterize its risk profile as one that "provides confidence" minimizes these risks and is therefore misleading. The brief disclosure of risk on the bottom of page 8 does not mitigate the misleading nature of this presentation.

Lack of Adequate Directions for Use

On page 9, the file card presents a 12-week, open-label, single-arm, historically controlled pilot study,[6] during which patients were treated with Exelon for up to 24 weeks before adding Namenda (memantine HCl). This presentation, which consists of a bar graph and a series of claims about the study, including claims about the patients' mean change in ADAS-Cog[7]

[5] According to the Drug-Drug Interactions section of the Exelon PI, based on *in vitro* studies, no pharmacokinetic drug interactions with drugs metabolized by the following isoenzyme systems are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.

[6] Riepe MW, Adler G, Ibach B, et al. Adding memantine to therapy with rivastigmine in patients with mild to moderate Alzheimer's disease: results of a 12-week pilot study [poster]. Presented at the 56th annual American Association of Neurology meeting; April 24-May 1, 2004; San Francisco, California.

[7] Alzheimer's Disease Assessment Scale Cognitive Subscale

score on this regimen and adverse events observed on this regimen, is misleading because the combination of Exelon and Namenda has not been proven to be safe and effective for the treatment of Alzheimer's Disease. These products are not indicated for use together as combination therapy; in fact, they are not indicated for the same patient populations (Exelon is indicated for mild to moderate dementia of the Alzheimer's type, while Namenda is indicated for moderate to severe dementia of the Alzheimer's type). This presentation thereby creates a new "intended use" for which the Exelon PI lacks adequate directions. While we note that the CLINICAL PHARMACOLOGY: Mechanism of Action section of the Exelon PI states, "*In vitro* and *in vivo* studies demonstrate that the inhibition of cholinesterase by rivastigmine is not affected by the concomitant administration of memantine, an N-methyl-D-aspartate receptor antagonist," this reference in the PI does not support claims of safety or efficacy for the unapproved combination of Exelon and Namenda therapy in the treatment of Alzheimer's Disease.

Conclusion and Requested Action

For the reasons discussed above, the file card misbrands Exelon in violation of the Act, 21 U.S.C. §§ 352(a) & (f)(1) & 321(n).

DDMAC requests that Novartis immediately cease the dissemination of violative promotional materials for Exelon such as those described above. Please submit a written response to this letter on or before August 22, 2007, stating whether you intend to comply with this request, listing all violative promotional materials for Exelon such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, or facsimile at (301) 796-9878. Please refer to MACMIS ID #14943 and NDA #20-823/21-025 in all future correspondence relating to this matter. DDMAC reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Exelon comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Abrams

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